

# Occupational Exposure to Pesticides and Pancreatic Cancer

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**Background** An increased risk of exposure to pesticides for pancreatic cancer has been suggested in a number of epidemiologic studies.

**Methods** Cases ( $N = 484$ ), aged 30–79 years, were diagnosed in 1986–1989. Controls ( $N = 2,095$ ) were a random sample of the general population. Information on usual occupation and potential confounding factors was obtained. A job-exposure matrix (JEM) approach was used to estimate the level of occupational exposure to pesticides.

**Results** A significant trend in risk with increasing exposure level of pesticides was observed, with ORs of 1.3 and 1.4 for low and moderate/high exposure levels, respectively. Excess risks were found for occupational exposure to fungicides ( $OR = 1.5$ ) and herbicides ( $OR = 1.6$ ) in the moderate/high level after adjustment for potential confounding factors. An increased risk for insecticide exposure was disappeared after adjustment for fungicide and herbicide exposures. Results of our occupation-based analysis were consistent with those from the JEM-based analysis.

**Conclusions** Our results suggest that pesticides may increase risk of pancreatic cancer, and indicate the need for investigations that can evaluate risk by specific chemical exposures. *Am. J. Ind. Med.* 39:92–99, 2001. Published 2001 Wiley-Liss, Inc.<sup>†</sup>

**KEY WORDS:** case-control study; job-exposure matrix; occupation; pancreatic cancer; pesticides

## INTRODUCTION

Some pesticides have been found to be carcinogenic in laboratory animals [Blair et al., 1990; Dich et al., 1997; Zahm et al., 1997]. In addition, excess risks for several human cancers have been observed in numerous epidemiological studies among farmers [Blair et al., 1992] and other occupational groups potentially exposed to pesticides [Zahm et al., 1997]. Based on these findings, IARC listed more than 20 insecticides, fungicides, and herbicides as probable or possible human carcinogens [IARC, 1991].

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Although two recent case-control studies of pancreatic cancer have indicated an increased risk associated with occupational pesticide exposure [Garabrant et al., 1992; Fryzek et al., 1997], the evidence linking pesticide exposures to the etiology of pancreatic cancer is limited. To examine associations of occupational exposure to pesticides (e.g., insecticides, fungicides, and herbicides) with pancreatic cancer risk, we conducted an analysis of data from a population-based case-control study among US whites and blacks.

## MATERIALS AND METHODS

We conducted a population-based case-control study of four malignant tumors that occur excessively in blacks (i.e., cancers of the pancreas, prostate, and esophagus and multiple myeloma) in three areas of the US. One general population control group was the source of controls for all four types of cancer. The current analysis was restricted to the carcinoma of the pancreas. Methods for this population-based case-control study have been described in detail elsewhere [Silverman et al., 1994, 1999]. Briefly, we included all cases with pancreatic cancer (ICD9 = 157) that were first diagnosed from August 1986 through April 1989 among 30–79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta (DeKalb and Fulton counties), Detroit (Macomb, Oakland, and Wayne counties), and New Jersey (10 counties). Most cases (85%) were diagnosed by tissue confirmation. An in-depth medical chart review was conducted to determine the accuracy of diagnosis of all cases, and 5.5% of them were excluded because they were found to be “unlikely” to have had pancreatic cancer. Since pancreatic cancer is a rapidly fatal disease, 471 of 1,153 patients initially identified for study died before the interview could be conducted. Of the 682 living cases identified for study, 526 (77%) were interviewed. A total of 41 interviewed cases were excluded from analysis because of an unlikely diagnosis of pancreatic cancer (16 cases), the presence of islet cell carcinoma (10 cases), no medical record available or an unsatisfactory interview (7 cases), and data unascertained for analysis (8 cases). Thus, 485 pancreatic cancer cases were included in the final analysis.

Controls were a stratified random sample of the general population of the study areas, frequency matched to the expected age-race-gender distribution of cases of the four types of cancer combined in each study area. Controls aged 30–64 years old were selected by random-digit dialing [Waksberg, 1978]. Of the 17,746 households telephoned, 86% provided a household census that served as the sampling frame for selection of controls under age 65 years. Of the 1,568 younger controls identified, 1,227 (78%) were interviewed. Controls aged 65–79 years were a stratified random sample drawn from the Health Care Financing

Administration rosters of the population age 65 or older in each study area. Of the 1,232 older controls selected, 926 (75%) were interviewed. Of the interviewed controls, 44 controls were excluded from analysis because of an unsatisfactory interview (7 controls) and data unascertained for analysis (37 controls). Thus, 2,109 controls were included in the final analysis.

Most subjects were interviewed in person at home. The questionnaire was used to obtain information on usual occupation/industry, as well as smoking habits, alcohol consumption, coffee and tea drinking, nutritional/dietary factors, medical conditions/interventions, family history of cancer, and socioeconomic status. Information on usual occupation and industry were coded according to the standard occupational classification (SOC) [U.S. Department of Commerce, 1980] and the standard industrial classification (SIC) [Executive Office of the President, 1972]. Results for all two-digit occupation groups are presented.

To assess occupational exposure to the three major groups of pesticides, i.e., insecticides, fungicides, and herbicides, we used a job exposure matrix (JEM) approach. The JEM for each class of pesticide was developed by an industrial hygienist (PAS). The JEM was based on an extensive review of the literature to identify where pesticides were used and what exposure levels have been measured. Based on this review, the level of exposure to each of the three pesticide classes was estimated for each study subject. The level of exposure on a 0–3 scale (0 = non-exposed; 1 = low level; 2–3 = moderate/high level of exposure) was assigned to the usual occupation of each subject. Selected occupations are shown in the Table I as samples for JEM scoring.

Odds ratios and 95% confidence intervals (CIs) for the pesticide and occupation group analyses were estimated by unconditional logistic regression analysis [Breslow and Day, 1980]. Race-specific ORs were adjusted for age at diagnosis (cases) or interview (controls), gender, study area, cigarette smoking, alcohol consumption, exposure to other pesticides, and income. Overall ORs also included adjustment for race. The specific effect of each pesticide class was also estimated with excluding subjects exposed to the other two classes of pesticides. A trend test for pesticide exposure level was performed by entering the exposure score as a continuous variable in the logistic regression model.

## RESULTS

Table II shows risk of pancreatic cancer associated with occupational exposure to any pesticides and to the major classes of pesticides: insecticides, fungicides, and herbicides. An increased risk was associated with any occupational pesticide exposure, with ORs of 1.3 (95% CI = 1.0–1.7) and 1.4 (95% CI = 1.0–2.0) for levels of low and moderate/high exposure, respectively, when compared to the risk among subjects whose usual occupation did not

**TABLE I.** JEM Scores for Selected Occupations

SOC	Job description	JEM scores (1–3)		
		Insecticides	Fungicides	Herbicides
5211	Supervisors, food and beverage preparation		1	
5216	Food counter, fountain and related occupations		1	
5342	Maids and housemen	1		
5244	Janitors and cleaners	1		
5512	General farmers	3		3
5513	Crop, vegetable, fruit and tree nut farmers	3	2	3
5612	General farm workers	3		3
5613	Field crop and vegetable farm workers	3		3
5621	Supervisors; related agricultural workers	3		2
5622	Ground keepers and gardeners	2		2
6910	Water and sewage treatment plant operators		2	
7658	Laundry and dry cleaning machine operators and tenders	2		
7659	Textile machine operators and tenders	2	2	
7664	Mixing and blending machine operators and tenders		3	3
7714	Welders and cutters	2		2

**TABLE II.** Odds Ratios for Pancreatic Cancer According to Level of Exposure to Insecticides, Fungicides, and Herbicides By Race

Level of exposure to pesticides (JEM)	Total				White				Black			
	No. of cases	No. of Controls	OR <sup>a,b</sup>	(95% CI)	No. of cases	No. of Controls	OR <sup>a</sup>	(95% CI)	No. of Cases	No. of Controls	OR <sup>a</sup>	(95% CI)
Any pesticide												
Non-exposed	293	1370	1.0		205	844	1.0		88	526	1.0	
Low	139	545	1.3	(1.0–1.7)	73	226	1.4	(1.0–1.9)	66	319	1.1	(0.7–1.5)
Moderate/high	52	180	1.4	(1.0–2.0)	29	79	1.4	(0.9–2.3)	23	101	1.2	(0.7–2.1)
( <i>P</i> for trend)				0.01				0.05				0.50
Insecticides <sup>c</sup>												
Non-exposed	376	1653	1.0		256	1000	1.0		120	653	1.0	
Low	45	201	0.5	(0.3–0.9)	19	49	0.9	(0.4–1.9)	26	152	0.3	(0.1–0.7)
Moderate/high	10	27	1.0	(0.4–2.5)	4	12	0.6	(0.2–2.9)	6	15	1.2	(0.4–3.9)
Fungicides <sup>c</sup>												
Non-exposed	332	1545	1.0		227	914	1.0		105	631	1.0	
Low	137	488	1.5	(1.1–1.9)	74	212	1.4	(1.0–1.9)	65	284	1.5	(1.0–2.3)
Moderate/high	2	8	1.5	(0.3–7.6)								
Herbicides <sup>c</sup>												
Non-exposed	439	1908	1.0		289	1089	1.0		150	819	1.0	
Low	14	40	1.5	(0.8–3.1)	9	19	1.7	(0.7–4.2)	5	21	1.2	(0.4–3.5)
Moderate/high	10	29	1.6	(0.7–3.4)	6	14	1.3	(0.5–3.7)	4	15	2.5	(0.7–8.2)

<sup>a</sup>ORs were adjusted for age at diagnosis/interview, study area, gender, cigarette smoking, income and alcohol consumption.<sup>b</sup>ORs were also adjusted for race.<sup>c</sup>ORs for the individual pesticides were also adjusted for the other two pesticide classes.

entail pesticide exposure. The exposure-response trend for any pesticide exposure was statistically significant ( $P$  for trend = 0.01). Initially, risks for insecticide exposure were 1.0 (95% CI = 0.7–1.4) and 1.9 (95% CI = 0.9–4.1) for subjects with low and moderate/high exposures, respectively (data not shown). However, after adjustment for fungicides and herbicides, increased risks for insecticides were no longer apparent (Table II). In contrast, ORs for fungicides and herbicides were not substantially altered after adjustment for insecticides and other classes of pesticides. The adjusted ORs for fungicides were 1.5 (95% CI = 1.1–1.9) and 1.5 (95% CI = 0.3–7.6) for low and moderate/high exposures, respectively, but the number of subjects in the moderate/high exposure category was small. Risks for herbicides were 1.5 (95% CI = 0.8–3.1) and 1.6 (95% CI = 0.7–3.4) among subjects with low and moderate/high exposures, respectively. No significant exposure-response gradient, however, was observed for fungicides and herbicides. Risk for pesticide exposure tended to be similar for blacks and whites, although a higher risk was observed for subjects with moderate/high exposure to herbicides among blacks (OR = 2.5) compared to whites (OR = 1.3). However, this difference based on small numbers of subjects was not statistically significant.

Since subjects who were exposed to insecticides also had a high probability of exposure to fungicides and/or herbicides (among controls the correlation coefficient ( $r$ ) = 0.44 between insecticides and fungicides, and  $r$  = 0.54 between insecticides and herbicides), further analyses were conducted to evaluate independent effects of each type of pesticide. No increased risk for pancreatic cancer was observed for insecticide exposure (OR = 0.5, 95% CI = 0.1–1.8) in those who were unlikely to have been occupationally exposed to fungicides and herbicides. In contrast, the excess risks from fungicide and herbicide exposures were not materially changed among those who were never occupationally exposed to insecticides (data not shown). Since exposures to fungicides may come from both agricultural and non-agricultural occupations, risks were examined by these two categories. No significant differences in risk were observed for fungicides exposure among agricultural (OR = 1.4, 95% CI = 0.7–2.7) and non-agricultural (OR = 1.5, 95% CI = 1.1–1.9) workers (data not shown). No dose-response trends were found with exposure duration (number of years worked at occupation with potential exposure), but a 50% excess was found among those who worked in an occupation with potential exposure to pesticides for more than 40 years (data not shown).

Risks for pancreatic cancer associated with usual occupation are presented in Table II. Non-significant increased risks were observed among subjects who were employed as farm operators and managers (OR = 2.2, 95% CI = 0.5–9.4), including crop, vegetable, fruit or tree nut farmers (OR = 2.5, 95% CI = 0.4–16.3) and in other

agricultural and related occupations (OR = 1.7, CI = 0.5–5.3), including farm/ground keepers and supervisors (OR = 2.0, 95% CI = 0.5–7.5). The associations were stronger among blacks than whites. For example, ORs for farm operators and managers were 9.2 (95% CI = 1.2–72.3) among blacks and 0.8 (95% CI = 0.1–7.3) among whites, and for crop, vegetable, fruit and tree nut farmers ORs were 6.1 (95% CI = 0.4–105) among blacks and 1.3 (95% CI = 0.1–14.8) among whites, but the number of exposed subjects in either race was small (data not shown). Elevated risks of pancreatic cancer were also seen for workers in the following occupations with possible exposure to insecticides and fungicides: food counter, fountain and related workers (OR = 1.7, 95% CI = 0.3–10.8); beverage preparation and service workers (OR = 1.2, 95% CI = 0.7–2.5); miscellaneous food and beverage workers (OR = 2.9, 95% CI = 0.5–16.1); cleaning and building service occupations (OR = 1.4, 95% CI = 0.8–2.6); and janitors and cleaners (OR = 1.5, 95% CI = 0.8–3.0) (data not shown).

Also shown in Table III are increased risks of pancreatic cancer for occupations where pesticide exposure was unlikely. Increased risks were associated with employment as pharmacists, dietitians, and therapists (OR = 7.1, 95% CI = 1.8–27.5); licensed practical nurses (OR = 2.9, 95% CI = 1.0–8.5); engineering and related technologists and technicians (OR = 1.3, 95% CI = 0.4–4.0) (including electrical and electronic engineering technologists and technicians (OR = 2.4, 95% CI = 0.6–10.2)); mechanics and repairers (OR = 1.4, 95% CI = 0.9–2.3) (including electrical repairers, commercial and industrial equipment workers (OR = 1.9, 95% CI = 0.5–7.6)); and plant (mainly power plant) and system operators (OR = 6.1, 95% CI = 1.1–33.9). Decreased risks were observed among officials and administrators (OR = 0.5, 95% CI = 0.3–0.9), management related occupations (OR = 0.7, 95% CI = 0.3–1.5), and private households occupations (OR = 0.7, 95% CI = 0.3–1.5). Racial comparisons in risk by occupational category were severely hampered by small numbers of exposed subjects.

## DISCUSSION

In this case-control study, we observed modest, marginally significantly increased risks for occupational exposure to pesticides. When risks were estimated by specific types of pesticides, elevated risks were apparent for fungicides and herbicides, but not for insecticides.

In 1992, Garabrant et al. [1992] reported a strong association between pancreatic cancer and occupational exposure to DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) (OR = 4.8, 95% CI = 1.3–17.6), DDD (1,1-dichloro-2,2-bis(4-chlorophenyl)-ethane) (OR = 4.3, 95% CI = 1.5–12.4), and ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl)ethane) (OR = 5.0, 95% CI = 1.4–18.2) in a nested

**TABLE III.** Odds Ratios for Pancreatic Cancer According to Usual Occupation

Occupation (two-digit SOC codes)	No. of Cases	No. of Controls	OR <sup>a</sup>	(95% CI)
Officials and administrators (11, 12, 13)	11	114	0.5	(0.3–0.9)
Supervisors and administrative support occupations (45, 46, 47)	77	228	1.2	(0.9–1.6)
Management related occupations (14)	8	57	0.7	(0.3–1.5)
Sales and marketing occupations (incl. insurance, security, and real estate) (40, 41, 42, 43)	30	150	0.9	(0.6–1.3)
Computer, mathematical, and operation research occupation (17)	1	15	0.4	(0.1–2.9)
Lawyers and judges (21)	2	8	1.9	(0.4–9.4)
Teachers, except postsecondary institute (23)	12	70	0.8	(0.4–1.6)
Private households occupations (50)	10	55	0.7	(0.4–1.5)
Protective service occupations (51)	7	28	1.2	(0.5–2.9)
Service occupations, except private household and protective service occupations (52)	50	182	1.2	(0.8–1.6)
Pharmacists, dietitians, and therapists (30)	5	4	7.1	(1.8–27.5)
Health technologists and technicians (36)	7	17	1.7	(0.7–4.3)
Farm operators and managers (55)	3	6	2.2	(0.5–9.4)
Other agricultural and related occupations (56)	4	14	1.7	(0.5–5.3)
Engineer, surveyors, and architects (16)	8	38	1.4	(0.6–3.2)
Engineering and related technologists and technicians (37)	4	17	1.3	(0.4–4.0)
Technicians, except health, engineering and science (39)	3	8	1.6	(0.4–6.4)
Mechanics and repairers (60, 61)	25	98	1.4	(0.9–2.3)
Construction trades (64)	19	73	1.2	(0.7–2.1)
Precision production occupations (67, 68)	20	85	1.0	(0.6–1.7)
Plant and system operators (69)	3	3	6.1	(1.1–33.9)
Production occupations (71)	6	36	0.9	(0.4–2.1)
Machine operators and tenders (76)	36	155	0.9	(0.6–1.4)
Fabricators, assemblers, and hand working occupations (77)	13	76	0.8	(0.4–2.7)
Production inspectors, checkers and examiners (78)	7	26	1.2	(0.5–2.8)
Transportation occupations (82)	19	115	0.8	(0.5–1.4)
Material moving occupations (83)	11	41	1.6	(0.8–3.3)
Handlers, equipment cleaners and laborers (87)	13	66	0.9	(0.5–1.6)

<sup>a</sup>ORs were relative to a risk of 1.0 for subjects whose usual occupation was not the specified occupation and were adjusted for age at diagnosis/interview, study area, gender, cigarette smoking, income, alcohol consumption, and race.

case-control study in a cohort of chemical manufacturing workers. Only 28 pancreatic cancer cases were identified in that study. However, a recent population-based case-control study based on 66 pancreatic cancer cases was conducted to further examine these associations [Fryzek et al., 1997]. Results suggested that self-reported exposures to ethylan, DDT and overall organochlorine pesticides were associated with an excess risk for pancreatic cancer, although estimates of risk were based on small numbers. In another nested case-control study, a significant 70% increased risk was reported for pancreatic cancer among subjects with exposure to insect or plant sprays 1 year before the interview [Friedman and van Den Eeden, 1993]. An excess risk of high serum level of DDE was diminished after adjustment for PCBs, although a significantly increased risk was associated with serum levels of polychlorinated biphenyls (PCBs) in a most recent case-control study [Hoppin et al., 2000]. A recent cohort study in the US found that aerial

pesticide applicators had a significant excess mortality from pancreatic cancer (rate ratio = 2.7, 95% CI = 1.4–5.3) when compared to flight instructors [Cantor and Silberman, 1999]. Several occupational studies have reported excess risks of pancreatic cancer among workers handling pesticides [Blair et al., 1993; Kauppinen et al., 1995], licensed agricultural pesticide users [Forastiere et al., 1993], gardeners [Partanen et al., 1994], nurserymen [Milham, 1997], yard-trash workers [Schwartz et al., 1998], flour mill workers [Alavanja et al., 1990], and corn wet-milling workers [Thomas et al., 1985]. However, excess risks were not observed in other studies of pesticide applicators or workers [Wong et al., 1984; Coggon et al., 1986; Wiklund et al., 1989; Brown, 1992] or among farmers or agricultural workers [Wiklund and Holm, 1986; Saftles et al., 1987; Burmeister, 1990; Blair et al., 1992; Franceschi et al., 1993; Pesatori et al., 1994], but some of those studies only had a small number of pancreatic cancer cases.

Results of our occupation-based analysis were consistent with results of the JEM analysis, as well as with findings in previous studies. We found that workers in occupations with potential exposure to pesticides, such as farmers, farm-related workers, food processing, and janitorial service workers, also had increased risks of pancreatic cancer. The excess risks remained unchanged after adjustment for some known risk factors, such as smoking, alcohol drinking, and social-economic status. Although these increased risks may be explained by other chemical agents or even by chance, pesticides may be potentially hazardous agents among workers in these occupations [Nigg et al., 1990].

In this study, the increased risks associated with exposures to fungicides and herbicides, but not to insecticides, were not compatible with the results of previous DDT-related studies. It is premature to conclude that pesticides are involved in the development of pancreatic cancer or that exposures to fungicides and/or herbicides may play a more important role than insecticide exposure. Nevertheless, our results add support to the evidence that pesticides may be related to pancreatic cancer.

Although an association between pesticide exposure and pancreatic cancer has not been established in human studies, pesticides have been shown to be carcinogenic in laboratory animals [Zahm et al., 1997]. Some pesticides are themselves genotoxic agents, which cause gene mutation or DNA rearrangements. Other pesticides, notably the organochlorines: DDT; chlordane; and lindane, are tumor promoters in animals. The phenoxyacetic acid herbicides can induce peroxisome proliferation which is related to carcinogenesis in rodents. Some organochlorines enhance human tumor development by mimicking the hormonal effects of estrogen; while other pesticides linking to human carcinogenesis may also be altering immune function [Dich et al., 1997; Zahm et al., 1997]. Although no biological mechanisms for pesticide carcinogenicity were studied specifically for pancreatic cancer, a Spanish case-control study found that elevated serum organochlorine levels were associated with K-ras mutations in pancreatic cancer [Porta et al., 1999].

The increased risk for other occupations observed in our study may provide clues to environmental causes of pancreatic cancer. The increased risks for pharmacists and licensed practical nurses have been previously reported [Kernan et al., 1999]. The high risks for mechanics and repairers/metal and plastic processing machine operators/tenders in our study were consistent with findings from some previous epidemiologic studies [Milham, 1976; Maruchi et al., 1979; Mallin et al., 1986; Silverstein et al., 1988; Siemiatycki et al., 1991; Ji et al., 1999]. Workers in these occupations could be exposed to a variety of industrial agents, including solvents, cutting oils, and metals. The excess risks of pancreatic cancer for electrical and electronic workers (e.g., electrical and electronic engineering

technologists and technicians; electrical repairers, commercial and industrial equipment workers; and power plant/system operators) have been also reported in previous epidemiological studies [Mack and Paganini-Hill, 1981; Mallin et al., 1989; Tynes et al., 1992; Yassi et al., 1994; Ji et al., 1999]. A mortality study in Canada found an excess for pancreatic cancer among transformer manufacturing workers who were extensively exposed to PCBs [Yassi et al., 1994], but the evidence is still insufficient.

Our study suffered from weaknesses that are typically found in case-control studies of occupation and cancer. First, small numbers of exposed subjects reduced the power to identify increased risks for specific occupations by race and gender, despite the large size of our study. Collapsing occupational sub-categories into broad categories may have diluted the risk estimates by combining jobs with and without hazardous exposures. Second, only information on usual occupation was available for analysis. Although missing short-term occupations may decrease sensitivity of exposure assessment, it typically does not reduce the specificity [Kauppinen et al., 1995]. Thus, if there is an effect of usual occupational exposure, it should be apparent. Third, since the JEM was based exclusively on the experience pertaining to the usual occupation instead of the subject's total exposure, some misclassification of exposure was likely to have occurred. Lack of information on year of employment in the usual job also weakens the accuracy of the exposure assignments in the JEM, because type and level of exposure changes with calendar time. The misclassification due to exposure assessment is likely to be non-differential and would tend to bias estimates towards the null. Last, since we only collected data on usual occupation and its duration, there are no data available on timing of the exposures. Thus, we could not examine risks by time period before the cancer occurred or since DDT was banned in 1979.

Our population-based case-control study has a number of strengths. First, the large number of cases and controls made it possible to evaluate risks of pancreatic cancer by detailed occupational categories. Second, unlike many other studies of pancreatic cancer, employment histories were obtained from direct interviews with the subjects rather than from next of kin, increasing the accuracy of information on usual occupation. Third, all risk estimates were controlled for the potential confounding effects of smoking and other risk factors (e.g., alcohol drinking, diet, and income). Finally, the JEM for pesticide exposure was specifically developed for this study population. Thus, it more closely reflects occupational exposure to pesticides in our cases and controls than a JEM developed for some other purpose, as is typical in case-control studies of occupation and cancer.

In conclusion, this population-based case-control study of pancreatic cancer in the three areas of the United States suggests a modest increased risk for occupational exposure to pesticides, particularly fungicides and herbicides, and for

workers employed in some pesticide-exposed occupations. Our findings add support to the evidence that pesticides may play a role in human pancreatic carcinogenesis. It does appear to be important to disentangle effects of different classes and specific kinds of pesticides on pancreatic cancer risk in the future studies.

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## REFERENCES

- Alavanja MCR, Blair A, Masters MN. 1990. Cancer mortality in the U.S. flour industry. *J Natl Cancer Inst* 82:840–848.
- Blair A, Axelson O, Franklin C, Paynter OE, Pearce N, Stevenson D, Trosko JE, Vainio H, Williams G, Woods J, Zahm H. 1990. Carcinogenic effects of pesticides. In: Baker SR, Wilkinson FC, editors: *The effects of pesticides on human health*. (Task Force of Environmental Cancer and Heart and Lung Diseases—Workshop, May 1988.) Princeton, NJ: Princeton Science Publishing, p 201–260.
- Blair A, Dosemeci M, Heineman EF. 1993. Cancer and other causes of death among male and female farmers from twenty-three states. *Am J Ind Med* 23:729–742.
- Blair A, Zham SH, Pearce NE, Heineman EF, Fraumeni JF Jr. 1992. Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 18:209–215.
- Brown D. 1992. Mortality of workers employed at organochlorine pesticide manufacturing plants—an update. *Scand J Work Environ Health* 18:155–161.
- Burmeister LF. 1990. Cancer in Iowa farmers: recent results. *Am J Ind Med* 18:295–301.
- Cantor KP, Silberman W. 1999. Mortality among aerial pesticide applicators and flight instructors: followup from 1965 through 1988. *Am J Ind Med* 36:239–247.
- Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. 1986. Mortality of workers exposed to 2-methyl-4-chlorophenoxyacetic acid. *Scand J Work Environ Health* 12:448–454.
- Dich J, Zahm SH, Hanberg A, Adami HO. 1997. Pesticides and cancer. *Cancer Causes Control* 8:420–423.
- Executive Office of the President. 1972. *Standard industrial classification manual*. Washington, DC: Office of Management and Budget, p 351–442.
- Forastiere F, Quercia A, Miceli M, Settimi L, Terenzoni B, Rapiti E, Faustini A, Borgia P, Cavarani F, Perucci CA. 1993. Cancer among farmers in central Italy. *Scand J Work Environ health* 19:382–389.
- Franceschi S, Barbone F, Bidoli E, Guarneri S, Serraino D, Talamini R, La Vecchia C. 1993. Cancer risk in farmers: results from a multi-site case-(hospital) control study in North-eastern Italy. *Int J Cancer* 53:740–745.
- Friedman GD, van Den Eeden S. 1993. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol* 22:30–37.
- Fryzek JP, Garabrant DH, Harlow SD, Severson RK, Gillespie BW, Schenk M, Schottenfield D. 1997. A case-control study of self-reported exposures to pesticides and pancreas cancer in Southeastern Michigan. *Int J Cancer* 72:62–67.
- Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. 1992. DDT and related compounds and risk of pancreatic cancer. *J Natl Cancer Inst* 84:764–771.
- Hoppin JA, Tolbert PE, Holly EA, Brock JW, Korric SA, Altshul LM, Zhang RH, Bracci PM, Burse VW, Needham LL. 2000. Pancreatic cancer and serum organochlorine levels. *Cancer Epidemiol Biomark Prev* 9:199–205.
- International Agency for Research on Cancer. 1991. Occupational exposures in insecticides application, and some pesticides. Lyon France: IARC: IARC monogr Eval Carcinog Risk Humans, Vol. 53.
- Ji BT, Silverman D, Dosemeci M, Dai Q, Gao YT, Blair A. 1999. Occupational and pancreatic cancer risk in Shanghai, China. *Am J Ind Med* 35:76–81.
- Kernan G, Ji BT, Dosemeci M, Silverman DT, Balbus J, Zahm SH. 1999. Occupational risk factors for pancreatic cancer: a case-control study based on death certificates from 24 U.S. States. *Am J Ind Med* 36:260–270.
- Kauppinen T, Partanen T, Degerth R, Ojajärvi A. 1995. Pancreatic cancer and occupational exposures. *Epidemiol* 6:498–502.
- Mack TM, Paganini-Hill A. 1981. Epidemiology of pancreas cancer in Los Angeles. *Cancer* 47:1474–1483.
- Mallin K, Berkeley L, Young Q. 1986. A proportional mortality of workers in a construction equipment and diesel engine manufacturing plant. *Am J Ind Med* 10:127–141.
- Mallin K, Ruin M, Joo E. 1989. Occupational cancer mortality in Illinois white and black males, 1979–1984, for seven cancer sites. *Am J Ind Med* 15:699–717.
- Maruchi N, Brain D, Ludwig J, Elveback LR, Kurland LT. 1979. Cancer of the pancreas in Olmstead County, Minnesota, 1935–1974. *Mayo Clin Proc* 54:245–249.
- Milham S. 1976. Cancer mortality patterns associated with exposure to metals. *Ann NY Acad Sci* 271:243–279.
- Milham S. Jr. 1997. Occupational mortality in Washington State, 1950–1989. DHHS (NIOSH) Publication No. 96–133.
- Nigg HN, Beier RC, Carter O, Chaisson C, Franklin C, Lavy T, Lewis RG, Lombardo P, McCarthy JF, Maddy KT, Moses M, Norris D, Peck C, Sknner K, Tardiff RG. 1990. Exposure to pesticides. In: Baker SR, Wilkinson FC, editors: *The effects of pesticides on human health*. (Task Force of Environmental Cancer and Heart and Lung Diseases—Workshop, May 1988.) Princeton, NJ: Princeton Science Publishing, p 35–130.
- Partanen T, Kauppinen T, Degerth R, Moneta G, Mearelli I, Ojajärvi A, Hernberg S, Kiskinen H, Pukkala E. 1994. Pancreatic cancer in industrial branches and occupations in Finland. *Am J Ind Med* 25: 851–866.
- Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. 1994. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida. *Cancer Causes Control* 5:310–318.
- Porta M, Malats N, Jarrod M, Grimalt JO, RifaJ, Carrato A, Guamer L, Salas A, Santigao-Silva M, Corominas JM, Andreu M, Real FX, et al. 1999. Serum concentrations of organochlorine compounds and K-ras mutation in exocrine pancreatic cancer. *The Lancet* 354:2125–2129.
- Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA. 1987. Cancer and other causes of death among Wisconsin Farmers. *Am J Ind Med* 11:119–129.

- Schwartz GG, Skinner HG, Duncan R. 1998. Solid waste and pancreatic cancer: an ecologic study in Florida, USA. *Int J Epidemiol* 27:781–787.
- Siemiatycki J, Gerin M, Dewar R, Nadon L, Lakhani R, Begin D, Richardson L. 1991. Associations between occupational circumstances and cancer. In: Siemiatycki J, editor. *Risk factors in the workplace*. Boca raton: CRC Press, p 142–145.
- Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, Brown LM, Greenberg RS, Hayes RB, Swanson GM, Wacholder S, Schwartz AG, Liff JM, Pottern LM. 1994. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. *J Natl Cancer Inst* 86:1510–1516.
- Silverman DT, Schiffman M, Everhart J, Goldstein A, Swanson GM, Schwartz AG, Brown LM, Greenberg RS, Schoenberg JB, Pottern LM, Hoover RN, Fraumeni JF, Jr. 1999. Diabetes mellitus, other medical conditions, and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 80:1830–1837.
- Silverstein M, Park R, Marmor M, Maizlish N, Mirer F. 1988. Mortality among bearing plant workers exposed to metal working fluids and abrasives. *J Occup Med* 30:706–714.
- Thomas TL, Krekel S, Heid M. 1985. Proportionate mortality among male corn wet-milling workers. *Int J Epidemiol* 14:432–437.
- Tynes T, Andersen A, Langmark F. 1992. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. *Am J Epidemiol* 136:81–88.
- U.S. Department of Commerce. 1980. *Standard occupational classification manual*. Washington, DC: Office of Federal Statistical Policy and Standards, p 18–31.
- Waksberg J. 1978. Sampling methods for random digit dialing. *J Am Stat Assoc* 73:40–46.
- Wilklund K, Dich J, Holm LE, Eklund G. 1989. Risk of cancer in pesticide applicators in Swedish agriculture. *Br J Ind Med* 46:809–814.
- Wilklund K, Holm LE. 1986. Trends in cancer risks among Swedish agricultural workers. *J Natl Cancer Inst* 77:657–664.
- Wong O, Brocker W, Davis HV, Nagle GS. 1984. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. *Br J Ind Med* 41:15–24.
- Yassi A, Tate R, Fish D. 1994. Cancer mortality in workers employed at a transformer manufacturing plant. *Am J Ind Med* 25:425–437.
- Zahm SH, Ward M, Blair A. 1997. Pesticides and cancer. *Occupational Med: State of the Art Review* 12:269–289.